REMARKS

The presently claimed invention relates to DNA probes having a region that includes: (a) at least one inosine residue; and (b) at least one nucleotide label. The region that includes the at least one inosine residue and the at least one nucleotide label does not hybridize to the target under specified high stringency conditions. As the specification explains, probes of this type are useful, in part, because they can exhibit reduced non-specific target binding compared to probes that do not include inosine residues.

Rejections Under 35 U.S.C. §103

The Examiner rejected claim 1 as obvious in view of O'Neil et al. (U.S. Patent No. 6,124,092) taken with Byng et al. (U.S. Patent No. 4,917,999). According to the Examiner, O'Neil et al. describes primers having a portion that does not hybridize to the target and is used as a "recovery tag" that can hybridize to its complement thereby facilitating isolation of elongated primers. The Examiner also states that O'Neil et al. discloses that "oligonucleotides may comprise non-naturally occurring backbones, analogs or naturally occurring polynucleotides, including, but not limited to inosine." According to the Examiner, Byng et al. discloses probes that include multiple inosine residues and various labels. The Examiner concludes that it would have been obvious to modify "the second region of the oligonucleotide of O'Neil et al. such that it comprised multiple inosinic residues as disclosed by Byng et al. as such would have afforded the artisan the ability to readily and reproducibly detect similar or related sequences with having to resort to the time, labor and expense of manufacturing additional probes."

Applicants respectfully traverse this rejection.

O'Neil et al.'s general reference to inosine residues does not suggest that the "recovery tag" should include inosine residues

The only mention of inosine in O'Neil et al. is in a general definition section at the end of column 4 where it is noted that the term oligonucleotide can include both naturally occurring polynucleotides and various analogs. This very general definition cannot reasonably be seen as a suggest that inosine be included in the recoverable primers, much less in the "recovery tag"

portion of the "recoverable primers" described by O'Neil. None of the examples of recoverable primers described by O'Neil include inosine.

O'Neil et al. teaches that the "recovery tag" should specifically bind to the "recovery tag binding compound"

O'Neil et al.'s recoverable primers include a "recovery tag" so the several different primers can be combined in a single sequencing reaction, for example, to sequence different portions of the same target molecule. In order to interpret the sequence ladders generated by the sequencing reaction, the extension products of each of the different primers must be isolated. The isolating is achieved by using a "recovery tag binding compound" that together with the recovery tag forms a "specific binding pair" (described at col. 5, lines 50-59). As O'Neil explains, the isolation of each recoverable primer is achieved by contacting the extension products with a solid support bearing the recovery tag binding compound and allowing specific binding between each recovery tag and the corresponding recovery tag binding compound.

> Each sequencing ladder is formed from a recoverable primer having a unique recovery tag. Every polynucleotide member of a polynucleotide set that constitutes a sequencing ladder is labeled with essentially the same recovery tag (or a functional equivalent of a recovery tag). After the simultaneous generation of multiple sequencing ladders, the different polynucleotide sequencing ladders are separated from one another by binding the recovery tags (or functional equivalents of recovery tags) to recovery tag binding compounds that have been immobilized on solid supports. The recovery tag binding compounds are immobilized on the solid support in an addressable manner, i.e., the recovery tag binding compounds have distinct locations on the solid supports or are located on separate distinct identifiable solid supports. The binding of the polynucleotide sequencing ladders to the recovery tag binding compounds serves to separate the different polynucleotide sequencing ladders

column 7, line 57 – column 8, line 8.

Thus, it can be seen that the formation of what O'Neil et al. describe as a "specific binding pair" composed of the recovery tag and the recovery tag binding compound is crucial. O'Neil describes a "specific binding pair" as follows:

> The term "specific binding pair" refers to a pair of molecules that specifically bind to one another. Binding between members of a specific binding pair is usually non-covalent. Examples of specific binding pairs include, but are not limited to

> antibody-antigen (or hapten) pairs, ligand-receptor pairs, biotin-avidin pairs, polynucleotides with complementary base pairs, and the like. Each specific binding pair comprises two members, however, it may be possible to find additional compounds that may specifically bind to either member of a given specific binding pair.

Col. 5, lines 40-49. To summarize, achieving the goals of the methods describe in O'Neil required using a recovery tag that specifically binds to the recovery tag binding compound.

Byng et al. teaches that inosine is useful for non-specific binding

Byng et al. describe a primer that is useful for detecting an α-amylase gene. Byng et al. based the sequence of the primer on a consensus amino acid sequence derived from several bacterial α-amylase protein sequences. In terms of designing the primer, the consensus amino acid sequence only allows one to identify the first two nucleotides in each codon since the third nucleotide can generally be one of at least two and sometimes three different nucleotides. Thus, to make a more universal primer, i.e., one that would recognize many α-amylase genes, Byng et al. used inosine as the third nucleotide in each codon. Byng et al. did this because inosine can base-pair with A, T, C or G. In other words, inosine is more non-specific in its binding to other nucleotides than is A, T, C or G. To summarize, Byng et al. teach the use of inosine when one wishes to have non-specific binding.

One would not be motivated to modify the recovery tag of O'Neil to include an inosine because doing so would create a recovery tag that is less capable of specific binding to the recovery tag binding compound

As discussed above, the method of O'Neil et al. relies on highly specific hybridization of each recovery tag to the corresponding recovery tag binding compound. Given the purpose of the recovery tag in O'Neil et al., one skilled in the art would not be motivated to modify the binding tag of O'Neil to include anything that could reduce the specificity of the binding of the recovery tag to the recovery tag binding compound. If one were to do so, the specificity of binding between the recovery tag and the recovery tag binding compound would decrease, making more difficult to isolate recoverable primers from a mixture of recoverable primers. Thus, making a modification to decrease specificity would defeat the very purpose of including a recovery tag in a primer.

As discussed above, Byng et al. teach the use of inosine when one wishes to have non-specific binding. Since the primers of O'Neil et al. depend on the presence of a recovery tag that is a specific binding partner for the corresponding recovery tag binding compound, one would not include an inosine in the recovery tag because Byng et al. teaches that inosine, which base-pairs with A, T, C or G decreases the specificity of binding. Thus, one skilled in the art would not modify the primers of O'Neil et al. to include inosines within the binding tag.

One would not be motivated to modify the recovery tag of O'Neil to include an inosine because doing so would create a recovery tag that is more likely to interfere with the ability of the template annealing sequence to bind to the template

As discussed above, inosine can base-pair with A, T, C, or G. Thus, it is less specific in its base-pairing than other nucleotides. Examiner stated that O'Neil teaches that the recovery tag should not interfere with the ability of the template annealing sequence to bind to the template. If this is true, than it is another reason that one of ordinary skill in the art would not want modify the primers of O'Neil et al. to include inosine into the recovery tag. Since inosine can base pair with A, T, C or G, incorporation of inosine would make it more likely that the recovery tag portion could hybridize to the template thereby interfering with the ability of the template annealing sequence to bind to the template.

The cited prior art teaches away from the present claims

As explained above, if one were one to introduce inosine residues into the recovery tag portion of the primer of O'Neil et al., the recovery tag would be less specific for hybridization to its complementary sequence and it would become more difficult to isolate each of the different primers. The ability to isolate different primers that have been combined in a single sequencing reaction is the goal of the methods described by O'Neil et al. Thus, far from encouraging the modification of the recovery tags of O'Neil et al. to include inosine residues, the cited references suggest to one skilled in the art that such a modification should not be made. Accordingly, the cited references amount to teaching away from the modification suggested by the Examiner. As the Court of Appeals for the Federal Circuit has explained "We have noted ... as a 'useful general rule,' that references that teach away cannot serve to create a prima facie case of obviousness." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339 (Fed. Cir. 2000). Thus, the

cited references cannot render claim1 obvious. In view of forgoing, Applicants respectfully request that this rejection under 35 U.S.C. §103 be withdrawn.

The Examiner's reasons for dismissing the argument that one would not incorporate inosine into the recovery tag of O'Neil et al. a misplaced

The Examiner cited two reasons for dismissing the argument that one would not incorporate inosine into the recovery tag of O'Neil et al for two reasons: a) "O'Neil et al. does teach using inosine residues in their oligonucleotide"; and b) there is no convincing evidence that the oligonucleotide of O'Neil does not hybridize under less specific conditions.

Regarding the Examiner's first reason, the very general statement in O'Neil et al. that simply defines oligonucleotides cannot be seen as a suggestion that inosine be included within the recovery tag portion of the primers. The detailed description of the requirements for a recovery tag, and not the general definition of a oligonucleotide, constitute the teachings regarding a recovery tag and the detailed description of the requirements for a recovery tag is not consistent with the inclusion of inosine. To maintain otherwise, as the Examiner appears to, amounts to improperly ignoring the teachings of the prior art reference.

The Examiner's second reason, given that the art teaches away from the modification of the recovery tag portion of the primers of O'Neil et al. to include inosine, the cited prior art cannot anticipate claim 1 irrespective of whether it can be concluded that the recovery tag of O'Neil et al. binds to the target nucleotide sequence.

Conclusion

In view of the forgoing, the Applicants respectfully request that the rejection of claim 1 under 35 U.S.C. §103, bewithdrawn

Rejections Under 35 U.S.C. §102

The Examiner rejected claim 11 as anticipated by GIBCO BRL Products & Research Guide ("GIBCO/BRL Catalog"), a catalog of products useful in biochemistry and molecular biology. The Examiner argued that claim 11 is anticipated because the various components of the claimed kit are offered for sale in the catalog and because claim 11 refers to a kit comprising the various components.

Applicants respectfully traverse this rejection.

While the GIBCO/BRL Catalog describes, among the hundreds of products offered, terminal transferase and various labeled and unlabeled nucleotides, it does not discloses terminal transfer and the nucleotides specified by claim 11 together in a kit, as required by claim 11. In view of this, the GIBCO/BRL Catalog cannot anticipate the kit of claim 11. It is irrelevant whether the claimed kit can include other components. The claim is not anticipated unless the prior art teaches a kit containing a minimum the listed components. While the Examiner asserts that the GIBCO/BRL Catalog lists the components specified in claim 11, the Examiner has failed to cite a reference teaching a kit containing the components. A catalog is not a kit. The GIBCO/BRL Catalog does disclose various kits containing various components, but the Examiner has not cited a teaching of a kit containing the components specified in claim 11.

In view of the forgoing, Applicants respectfully request that this rejection under 35 U.S.C. §102(b) be withdrawn.

Enclosed is a Petition for Extension of Time with the appropriate fee. Please apply any other charges or credits to deposit account 06-1050.

Respectfully submitted,

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